MicroRNAs serve as a bridge between oxidative stress and gastric cancer (Review)

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Abstract. Gastric cancer (GC) remains one of the most prevalent tumors worldwide and affects human health due to its high morbidity and mortality. Mechanisms underlying occurrence and development of GC have been widely studied. Studies have revealed reactive oxygen species (ROS) generated by cells under oxidative stress (OS) are involved in gastric tumorigenesis, and modulate expression of microRNAs (miRs). As such, miRs have been shown to be associated with OS-related GC. Given the association of OS and miRs in development of GC, this review aims to summarize the relationship between miRs and OS and their role in GC development. Serving as a link between OS and GC, miRs may offer new approaches for gaining a more in-depth understanding of mechanisms of GC and may lead to the identification of new therapeutic approaches against GC.

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1. Introduction

Gastric cancer (GC) is one of the most common types of cancers worldwide. Each year, almost one million people are newly diagnosed with GC, and over 700,000 people die of GC (1). Due to high prevalence and death rate, GC remains a tremendous threat to word health. An increasing body of evidence shows that patients with GC experience high levels of OS, which contribute to progression of GC. Markers of OS, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), human oxoguanine glycosylase 1 (hOGG1) and xanthine oxidase (XOD) are aberrant in GC (2). Due to redox imbalance, OS

participates in progression of GC by affecting expression of critical effectors, including miRs (3,4). miRs are small non-coding RNAs that modulate gene expression by either inhibiting mRNA translation or inducing mRNA degradation at post-transcriptional level (5). miRs have been relevant to promotion or suppression of tumorigenesis in GC and are implicated in cell growth, differentiation, invasion, metastasis, and apoptosis in GC (6). Additionally, OS gives rise to abnormal expression of miRs in various types of diseases, including cancers (7-9). Although function of miRs has been extensively investigated in GC, whether miRs may be associated with or serve as a link between OS and GC remains unknown. In this review, we focus on roles of OS in GC, OS-induced miRs in GC, and roles of dysfunctional miRs in GC to gain further understanding of the association of OS and miRs in gastric tumorigenesis.

2. OS is involved in the tumorigenesis of GC through ROS

OS, which refers to redox imbalance with excessive production of ROS exceeding the scavenging ability of human body (10), has been associated with pathophysiology of both solid tumors and hematological malignant diseases (11,12). ROS, including superoxide ($O_2^{\bullet-}$), hydroxide ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2), lead to damage to cell membrane, protein, and DNA (13). Physiologically, glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase could scavenge ROS to preserve redox homeostasis. ROS also contribute to cell apoptosis by regulating p38α mitogen-activated protein kinases (MAPK) (14). More importantly, ROS stimulate the NF-E2-related factor (NRF2)-mediated activation of an anti-oxidant response element (ARE) to protect cells again OS (15). Nevertheless, under OS, excessive ROS in cells could damage tissues, leading to tumorigenesis, particularly in the gastrointestinal tract.

For GC, in both human and mouse, ROS are actuated factors in gastric carcinogenesis. In human GC, ROS are dysregulated in serum and tissue samples (16). In *Helicobacter pylori* (Hp) along with N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) triggered mouse GC models, ROS activated downstream targets including P53, Wnt, Ras, mTOR to initiate gastric carcinogenesis (17,18). Hypoxia leads to producing ROS, which prevent degradation of hypoxia-inducible factor 1α (HIF-1α) (19). As a transcription factor, accumulation of HIF-1α is able to modulate expression of various genes, which are important in gastric tumorigenesis. For example, HIF-1α attenuates expression of caveolin-1 (Cav-1), which can induce the epithelial-mesenchymal transition (EMT) in GC through regulation of E-cadherin (20). HIF-1α also activates vascular endothelial growth factor (VEGF) pathway to enhance angiogenesis in GC (21). In contrast, ROS act as a signaling molecule and trigger essential signaling pathways indispensible to promoting the occurrence and development of GC. As second messenger, ROS are well known to activate tyrosine kinases and MAPK, leading to cell proliferation (22), as well as trigger activation of protein kinase-B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway to promote GC cell proliferation (23). Moreover, ROS have been found to stimulate nuclear factor-κB (NF-κB) to promote GC invasion (24,25).

In addition, OS exerts a crucial role in Hp-induced diseases. Hp infection is a recognized risk factor in pathogenesis of gastric disease, such as chronic atrophic gastritis, gastric ulcer, and GC. Chaturvedi *et al* showed that Hp activation of spermine oxidase (SMOX) in gastric epithelial cells results in OS (26). OS causes damage to biological structures such as proteins, carbohydrates, lipids, and nucleic acids (27). DNA damage promotes activation of the epidermal growth factor receptor (EFGR) signaling pathway and mutations of tumor-suppressor genes, such as p53 and calcium/calmodulin-dependent serine protein kinase (CASK) (28,29), which are critical initial events in gastric carcinogenesis. Additionally, Hp infection also induces changes in expression of miRs in GC. For example, miR-328 is a well-studied miR involved in Hp-induced GC. Ishimoto *et al* demonstrated that miR-328 is downregulated in Hp-infected gastritis (30). Analysis of expression of miR-328 in GC, yielded a result similar to that obtained in gastritis. A low level of miR-328 activates CD44, a target of miR-328, to promote GC stem cell differentiation (4). Effect of Hp infection on miR-328 expression could be mimicked by H_2O_2. Therefore, miR-328 may be a specific miR that triggers development of Hp-induced GC by ROS. However, these researchers did not provide an explanation for downregulation of miR-328 in Hp-infected GC. Indeed, previous studies have demonstrated that Hp induced expression miR-210 by regulating methylation of miR-210, thereby increasing proliferation of gastric epithelial cells through suppressing oncoprotein 18 or metablastin (STMN1) and dimethyladenosine transferase 1 (DIMT1) (31). Therefore, Hp infection may alter expression of miRs through ROS-mediated methylation of gene promoter region. Hp-induced OS, which interferes with methylation of miRs, may account for part of the mechanism underlying the initiation of GC. In studies of effect of radiation on GC cells, radiation, which acts similarly to OS, also leads to production of ROS (32).

In conclusion, hypoxia, Hp infection, and radiation are capable of triggering cellular OS, and excessive ROS lead to the inhibition of anti-oncogenes such as p53, and the activation of tumorigenesis-associated signaling pathways, which contribute to occurrence and development of GC (Fig. 1).

3. OS modulates expression of miRs

Since the first miR, lin-4 (3), was discovered, an increasing number of studies have focused on these small non-coding RNAs. miRs regulate gene expression by completely or incompletely binding to 3' untranslated region (3'-UTR) of target messenger RNAs. miRs are demonstrated to modulate expression of target genes. However, the crucial factor affecting expression of miRs has not been identified. OS can influence gene expression by regulating their methylation status of genes (33,34). Whether OS can affect the expression of miRNAs remains an open question.

As mentioned previously, under OS, ROS are produced and play a key role under pathological conditions. Hydrogen peroxide is widely used in experiments to simulate the effect of OS in cell lines and results in the abnormal expression of miRs in numerous diseases, including vitiligo, idiopathic pulmonary fibrosis (IPF), and most cancers. ROS induced miR-25 has been shown to enhance degeneration of melanocytes in
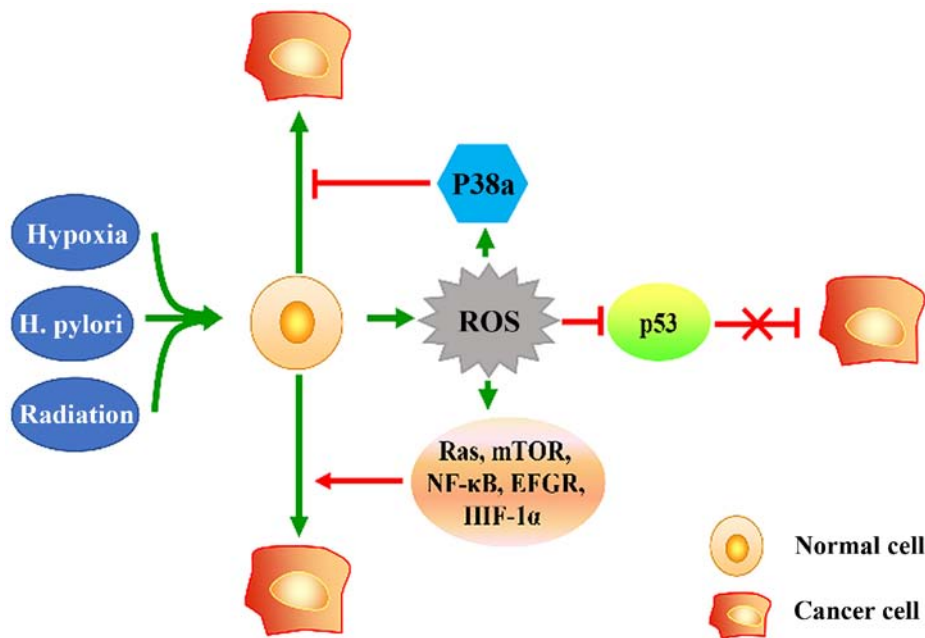
Figure 1. Effect of OS on gastric cells. Hypoxia, Hp infection, and radiation lead to OS. Product of OS, ROS activate p38α in response to OS to act as an adaptive change for the prevention of tumorigenesis. Excessive ROS lead to the activation of Ras, mTOR, NF-κB, EFGR, and HIF-1α to trigger development of GC, and the mutation of P53, loss of expression of which also contributes to gastric tumorigenesis.

vitiligo (35). Elevated levels of miR-9-5p has been confirmed to be influenced by ROS both *in vivo* and *in vitro*. In specimens of patients with IPF, expression of miR-9-5p has been associated with ROS and is upregulated in human fetal lung fibroblasts treated with hydrogen peroxide (36). Independently, endoplasmic reticulum (ER) stress can be caused by hypoxia, failure of protein maturation, or degradation (37). Induced by ER stress, expression of miR-17, -34a, -96, and -125b and the consequent reduction in the translation of proapoptotic caspase-2 (38). Additionally, exposure of cells to arsenic triggers upregulation of miR-663, miR-222, and miR-638 (39).

ROS exhibit their characteristics in intervening in expression of miRs in cancers. Similarly, placing cells under hypoxic condition is a common way to test the effect of OS on cancer cell lines. In breast and prostate cancer cells, miR-196b could be restrained by hypoxia (40). In bladder cancer cells, hypoxia could induce expression of miR-145 (41). Additionally, in response to ionizing radiation, ROS were stated to upregulate miR-193a-3p and miR-30e (42,43). miR-193a-3p has been demonstrated to lead to apoptosis by targeting Mcl-1, and miR-30e promote glioma cell invasion through EGFR stabilization by directly targeting Casitas-B-lineage lymphoma (Cbl)-b.

In GC, miR-382 was upregulated by hypoxia and participate in hypoxia-induced angiogenesis of GC (44). As discussed previously, Hp infection alters expression of miRs, such as miR-328 and miR-210, through ROS. Moreover, our team and other researchers focused on activities of miR-21 in GC and concluded that ROS give rise to progression of GC through dysfunction of miR-21 (45,46). Both programmed cell death protein 4 (PDCD4) and phosphatase and tension homolog deleted on chromosome 10 (PTEN) have been confirmed to be targets of miR-21. The silencing of miR-21 with its inhibitor AC1 MMYR2 reverse the effect of EMT accompanied by

suppression of proliferation and invasion of GC (47). We also sought to identify other miRs affected by ROS ($O_2^{\cdot-}$, $^{\cdot}OH$); but few studies have examined the relationship of $O_2^{\cdot-}$ and $^{\cdot}OH$ with miRs because H_2O_2 is easy to use and detect in experiments. However, we found that enzymes catalyzing $O_2^{\cdot-}$ and $^{\cdot}OH$ are positively correlated with the expression of some miRs, such as miR-200b (48). In fact, the role of OS in regulating the expression of miRs has been widely studied. Selected miRs responsive to OS are shown in Table I. In summary, under OS, product of OS in cells mediate expression of miRs by different mechanisms and participate in progression of various types of diseases, including GC. The detailed mechanism will be discussed in part 5.

4. Alteration of miRs participates in tumorigenesis of GC

It is well known that miRs are differentially expressed in different types of cancers and are implicated in processes of carcinogenesis, such as cell proliferation, angiogenesis, invasion, and metastasis. miRs have been identified to predict prognosis of GC patients. For example, selective overexpression of miR-25 in advanced GC indicated poor survival (58) and downregulation of miR-451 was associated with worse prognosis of GC patients (59). miRs may regulate the cell cycle through direct interaction with key regulators, such as cyclin, cyclin-dependent kinase (CDK), and cyclin-dependent kinase inhibitor (CDI). Specifically, cyclins D1 and E1 are targets of miR-16, and low levels of miR-16 contribute to development of colon cancer (60). In leukemia, CDK2 has been found to be a target gene of miR-638, and depression of miR-638 was found to be crucial for differentiation and proliferation of leukemia cells (61). With regard to miR-related cancer invasion and metastasis, miR-367 has been shown to promote invasion by downregulating Smad7 and to stimulate the EMT through

Table I. OS regulates expression of miRs.

Items	miRs	Expression	Induced by	Refs.
Gastric cancer	miR-370	Downregulated	*H. pylori*	(49)
	miR-203	Downregulated	*H. pylori*	(28)
	miR-328	Downregulated	*H. pylori*, H_2O_2	(4,50)
Lung fibrosis	miR-9-5p	Upregulated	H_2O_2	(36)
Vitiligo	miR-25	Upregulated	H_2O_2	(35)
Mesenchymal stem cells	miR-181a	Upregulated	H_2O_2	(51)
Endothelial innate immune response	miR-92a	Upregulated	H_2O_2	(52)
MELAS syndrome	microRNA-9/9*	Upregulated	H_2O_2	(53)
Cardiac muscle, vascular smooth muscle cells	miR-30 family	Downregulated	H_2O_2	(54)
Glioma	miR-193a-3p	Upregulated	Radiation	(42)
	miR-30e	Upregulated	Radiation	(43)
Human bronchial epithelial cells	miR-15b/16-2	Upregulated	Radiation	(55)
Nasopharyngeal carcinoma	miR-504	Upregulated	Radiation	(56)
Bladder cancer	miR-769-3p	Downregulated	Hypoxia	(57)
	miR-145	Upregulated	Hypoxia	(41)
Breast and prostate cancer	miRNA-196b	Downregulated	Hypoxia	(40)

activation of the transforming growth factor-β (TGF-β) signaling pathway (62). Moreover, in chondrosarcoma, miR-200b directly repress VEGF to inhibit angiogenesis (63). In cancers, most decreased miRs show activities as tumor-suppressor gene, and miR mimics prevent development of cancer. Conversely, high levels of miRs mainly act as oncogene and promote tumorigenesis. Following this review of role of miRs in cancer, we will concentrate our discussion on roles of miRs in GC.

In GC, numerous miRNAs have been identified, and dysfunction of these miRs promotes progression of GC. Expression of miRs has been found to be either increased or decreased in both GC tissues and cell lines. For example, miR-133b/a-3p has been ascertained to be reduced in primary GC tissues and two GC cell lines, namely SGC7901 and MNK45 (64). Using TargetScan database and luciferase assay, myeloid cell leukemia 1 (Mcl-1) and BCL2-like 1 (Bcl-xL) were shown to be targets of miR-133b/a-3p. Furthermore, using mouse tumor-bearing model and cell lines, miR-133b/a-3p has been ascertained to inhibit tumor growth. Similarly, miR-940 has been shown to promote tumor cell invasion and metastasis by interacting with zinc finger transcription factor 24 (ZNF24) in GC (65); miR-130a and miR-495 have been confirmed to increase cell proliferation and angiogenesis by targeting runt-related transcription factor 3 (RUNX3) in GC (66); miR-544a could induce the EMT by sensitizing Wnt signaling pathway in GC (67); and a lower miR-100 level is associated with lymphatic metastasis by targeting zinc finger and BTB domain containing 7A (ZBTB7A) (68). In fact, miRs have been widely investigated in GC. Studies of miRs in GC almost follow the methods described above. A list of miRs in GC, including their expression types, targets, and functions in gastric cancer is presented in Table II. Similar to role of miRs in other types of cancers, increased levels of miRs in GC act as

oncogenes and reduced levels of miRs act as tumor suppressor genes. In general, molecules downstream of these miR targets are key factors involved in the signaling pathways in GC. For example, miR-141 is capable of regulating EGFR2 signaling pathway to affect proliferation of GC cells (69), and miR-495 can influence migration and invasion by action of phosphatase on regenerating liver-3 (PRL-3) (70); and Kip1 (p27), acting as a CDK, is the direct target of miR-196a, and a lower level of Kip1 due to inhibition by miR-196a leads to the proliferation of GC cells (71).

Few studies have evaluated screening or diagnostic value of miRs in gastric juice and serum as a noninvasive method for GC treatment. The miR-21 and miR-106a levels in gastric juice were lower in GC than in benign gastric diseases, and showed a specificity of 0.969 and 0.871, respectively, for the identification of GC compared with benign gastric diseases (88). In GC, serum level of miR-203 is significantly lower compared with the control. Similar to its value in GC tissue, lower serum levels of miR-203 reflect an advanced clinical stage and poor overall survival, which is consistent with well-studied activity of miR-203 in inhibiting the EMT (89,90).

Despite the roles of these miRs, few studies have compared levels of miR in both tissue and serum from time of occurrence of morbidity to time of death of GC patients. This question is challenging for several reasons, such as the fact that we may not know when GC begins and cannot obtain adequate tissue samples once tumor progresses. By studying changes in the levels of miRs in body fluids, it may be possible for us to identify specific markers for GC.

5. miRs serve as a link between OS and GC

As discussed above, product of OS is involved in development of GC, and production of OS thus leads to an abnormal

Table II. Alteration, function, and target(s) of some miRs in gastric cancer.

miRs	Expression	Target (s)	Function	Refs.
miR-7	Downregulated	RELA, FOS	Inhibition of proliferation	(72)
miR-100	Downregulated	ZBTB7A	Inhibition of proliferation and metastasis	(68)
miR-141	Downregulated	EGFR2	Inhibition of proliferation	(69)
miR-182	Downregulated	CREB1	Inhibition of proliferation	(73,74)
miR-100	Downregulated	HS3ST2	Inhibition of proliferation	(75)
miR-409-3p	Downregulated	RDX, PHF10	Inhibition of proliferation, invasion, and metastasis	(76,77)
miR-124	Downregulated	SPHK1	Inhibition of proliferation	(78)
miR-495/551a	Downregulated	PRL-3	Inhibition of migration and invasion	(70)
miR-625	Downregulated	ILK	Inhibition of invasion and metastasis	(79)
miR-145	Downregulated	CDH2	Inhibition of invasion, metastasis, and angiogenesis	(80)
miR-874	Downregulated	STAT3	Inhibition of angiogenesis	(81)
miR-21	Upregulated	RECK, PTEN, PDCD4, TPM1, Maspin	Promotion of proliferation and metastasis	(82-84)
miR-301a	Upregulated	RUNX3	Promotion of proliferation and metastasis	(85)
miR-196a	Upregulated	KIP1	Promotion of proliferation	(71)
miR-296-5p	Upregulated	CDX1	Promotion of proliferation	(86)
miR-223	Upregulated	EPB41L3	Promotion of invasion and metastasis	(87)

Table III. Expression of miRs is modulated by epigenetic factors in GC.

miRs	Expression	Methylation status	Modulated by	Refs.
miR-200b/a/429	Downregulated	Hypermethylation	DNMT1/EZH2	(95)
let-7	Downregulated	Hypermethylation, H3K27 trimethylation	DNMT3B/EZH2	(101)
miR-99a/449a	Downregulated	H3K27 trimethylation	EZH2	(102)
miR-124a-1/2/3	Downregulated	Hypermethylation	NA[a]	(100)
miR-139	Downregulated	Hypermethylation	NA	(103)
miR-490-3p	Downregulated	Hypermethylation, H3K4 trimethylation	NA	(104)
miR-335	Downregulated	Hypermethylation	NA	(105)
miR-34b/c	Downregulated	Hypermethylation	NA	(106)
miR-200b	Downregulated	Hypermethylation	NA	(107)
miR-149	Downregulated	Hypermethylation	NA	(94)
miR-196b	Upregulated	Hypomethylation	NA	(99)
miR-127	Upregulated	Demethylation	NA	(100)

[a]NA, not available.

expression profile of miRs in diseases including cancers. Importantly, miRs can either promote or suppress tumorigenesis in GC. Whether miRs may serve as a link between OS and GC remains unclear.

To the best of our knowledge, epigenetic factors play a crucial role in carcinogenesis during OS. ROS contribute to methylation of miR genes, subsequently resulting in development of cancer by influencing expression of miRs, such as miR-145-5p, miR-362-3p, miR-329, miR-199, and miR-125 (91-93). Frequently, ROS increase methylation of miRs, which play roles of tumor suppressor genes. For example, the hypermethylation of miR-199a and miR-125b induced by ROS is modulated by DNA methyltransferase (DNMT) 1, which downregulated these two miRs in an ovarian cancer cell line (93).

In Hp-induced GC, a decreased expression of miR-328 is mediated by ROS (4). Expression of miR-210 and miR-149 is thought to be modulated by methylation in Hp-positive human gastric biopsies (31,94). Hypoxia also leads to alteration of miR expression in GC. For example, miR-495 is upregulated under hypoxic conditions in two gastric cell lines, SNU5 and SNU484 (66), and methylation of corresponding promoter
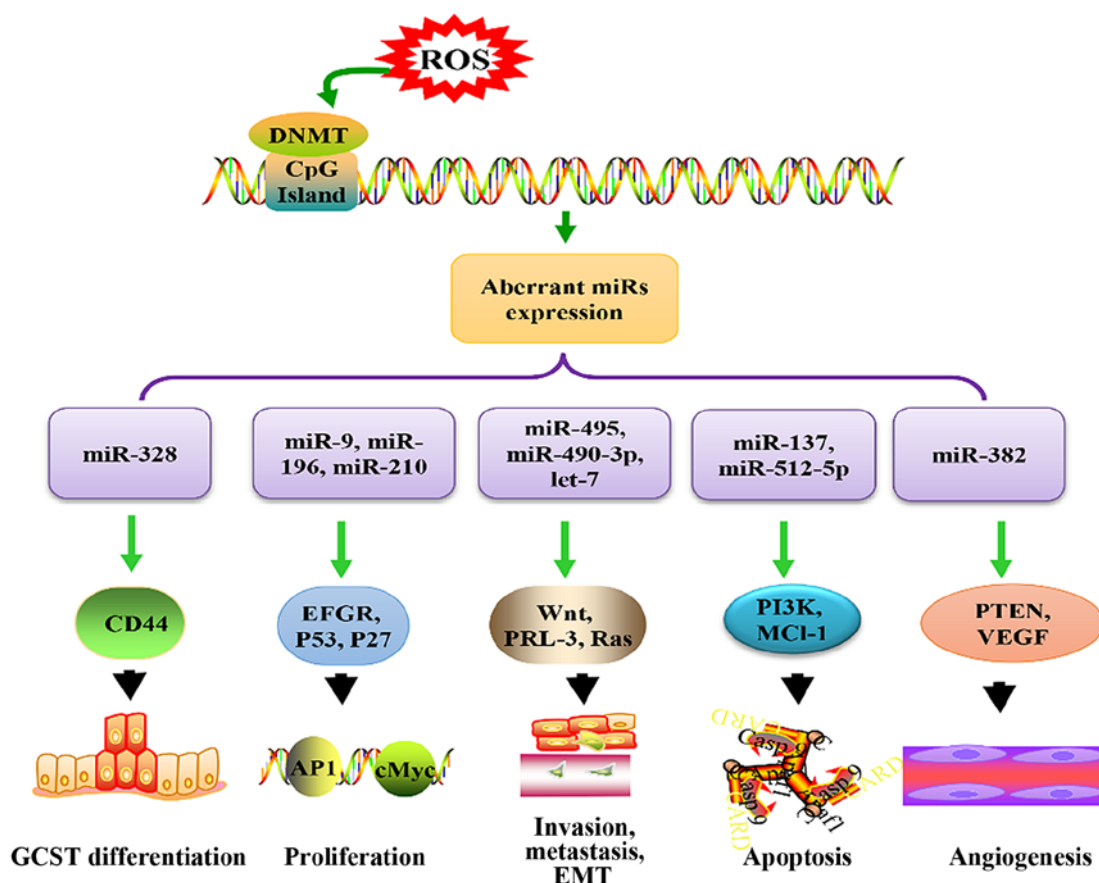
Figure 2. OS-related miRs in development of GC. ROS affect changes in DNMT, thereby contributing to aberrant miR expression. In GC, targets of miRs are involved in gastric cancer stem cell differentiation through CD44, the proliferation of GC through the VEGF signaling pathway, cell cycle regulation through p53, the EMT though the Wnt signaling pathway, apoptosis by the PI3K signaling pathway, and invasion and metastasis through PRL-3.

region contributes to dysregulation of miR-495 in GC. Following inhibition by DNMT1 and Zeste homolog 2 (EZH2), a repressed level of miR-200b/a/429 leads to progression of GC (95). The methylation-mediated silencing of miR-9 family in a GC cell line and the patient specimens was confirmed by combined bisulfate restriction analysis (COBRA) (96). Importantly, treating cells with 5-aza-2'-deoxycytidine (5-aza-CdR) reverses this action. Similarly, methylation of miR-137 gradually increases in normal gastric tissue, chronic gastritis, and GC tissue (97), and treatment of GC cell lines with 5-aza-CdR and 4-phenylbutyric acid (PBA) activates previously silenced miR-512-5p, causing its raised levels to induce cell apoptosis (98). Collectively, miRs are frequently dysregulated in GC (Table III). Interestingly, levels of most miRs are decreased by hypomethylation, but only two miRs, namely miR-196b and miR-127, have been identified to be elevated by hypomethylation in GC (99,100).

Actually, ROS-mediated deregulation of DNA methylation is quite an important aspect of biological role of ROS. ROS-mediated elevation of 8-OHdG in CpG island is one of the major mechanism of ROS-mediated hypomethylation, however, some form of ROS induced DNA damage also stimulate DNA methylation of specific loci. DNA hypermethylation of promoter region of genes is known to result in gene silencing, whereas hypomethylation contributes to increased gene expression. In GC, ROS induce expression of HIF-1α (19), which increases expression of DNMT enzymes DNMT1

and DNMT3B, resulting in gene silencing through gene hypermethylation (108). Interestingly, HIF-1α can also result in hypomethylation of genes by regulating MAT1A/MAT2A switch (109). By contrast, expression of miRs could also be modulated by histone deacetylases (HDACs). For example, miR-466 h-5p is elevated when histone deacetylation is inhibited by glucose deprivation-induced OS (110).

In conclusion, this review infers that in GC, ROS lead to changes in DNMT, which results in methylation changes in promoter region of miR genes that play roles in development of GC through inhibition of their targets and related signaling pathways (Fig. 2).

6. Conclusion

We summarized changes of OS as well as miRs and analyzed their function in gastric carcinogenesis. We conclude that ROS and parts of miRs exhibit overlapped characters in gastric carcinogenesis. Given that ROS mediate expression of miRs through epigenetic mechanism, we predict miRs serve as a bridge between ROS and gastric cancer. ROS are the driving force for gastric carcinogenesis. In both human and mouse gastric cancer models, ROS triggered crucial signal pathways and vital molecules such as Wnt, ERK, P53, and miRs to induce initiation and development of GC. In Hp-positive GC patients as well as Hp evoked mouse model of GC, ROS are also confirmed dysfunctional. While, we must accept that in

treatment of GC, most drugs function through ROS-activated apoptosis of tumor cells, and some researchers found anti-oxidant can promote progress of cancer cells. Activities of ROS levels were dependent on cancer cells. How to define the threshold of ROS may be an important approach to identify their function in cancer cells. miRs are hot topics in cancer research. Diverse miRs change in GC making them hard to be specific targets in treatment of GC. However, detection of miRs in body fluid and tissues will be a treatment reaction or prognostic factor. miR expression profiling studies make it possible for us to probe miR change in different tissues or body fluid. Despite the encouraging prospect, we are still faced with many difficulties in the fields of OS-induced miRs in GC, tumor-related miRs, signaling pathway network between OS and gastric cancer and interaction between them. Expression of miRs presents tissue, time, and space specificity and can be affected by a variety of factors, which makes it hard to iden-tify a consistent miRNA signature with high specificity for diagnosis and prognosis purpose. Furthermore, miRs exert a limited role in complex gene regulation network and modulate expression of multiple genes, suggesting complexity of miR function and both the potentially limited and undeliberate effect of therapy targeted to a limited number of miRs.

Acknowledgements

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